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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,594	NAZARENKO ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,14,15,17-22,59,63-67 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,14,15,17-20,59 and 63-67* is/are rejected.

7)☒ Claim(s) *21,22 and 76-79* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by Horn et al (U.S. Patent 6,465,175).

Horn teaches a method of claim 20 for quantification of target nucleic acid molecules in a sample comprising:

(a) Mixing one or more target nucleic acid molecules with one or more fluorescently labeled oligonucleotides (see column 3, lines 7-20),

Wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure (see column 3, lines 7-20, where only a single label is used)

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 3, lines 7-20, where the label is fluorescent when the probe is single stranded by is quenched when hybridized). In particular, Horn shows in example 1 at columns 13 and 14, that the BODIPY FL label was capable of being quenched by hybridization when it was directly linked to the probe, but not when it

was linked via a linker which rendered it distant from the hybridization. In example 3 at columns 15 and 16 and in figure 1, Horn shows quenching with multiple labels with the same chemical structure, that of BODIPY FL. Horn makes the use of a single label explicit in example 5, where a modified Taqman assay is taught in which an oligonucleotide singly labeled with BODIPY FL is used without the use of a quencher dye (see column 17, lines 50-55).

(b) Incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to a portion of said one or more target nucleic acid molecules (see columns 17 and 18)

(c) detecting the presence or absence or quantifying the amount of the target molecules by measuring the fluorescent label (see columns 17 and 18).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 11, 12, 14, 15, 17-20, 59 and 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn et al (U.S. Patent 6,465,175) in view of Tyagi et al (U.S. Patent 6,037,130).

Horn teaches a method of claims 11 and 12 for quantification of target nucleic acid molecules in a sample comprising:

(a) Mixing one or more target nucleic acid molecules with one or more fluorescently labeled oligonucleotides (see column 3, lines 7-20),

Wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure (see column 3, lines 7-20, where only a single label is used)

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 3, lines 7-20, where the label is fluorescent when the probe is single stranded by is quenched when hybridized). In particular, Horn shows in example 1 at columns 13 and 14, that the BODIPY FL label was capable of being quenched by hybridization when it was directly linked to the probe, but not when it was linked via a linker which rendered it distant from the hybridization. In example 3 at columns 15 and 16 and in figure 1, Horn shows quenching with multiple labels with the same chemical structure, that of BODIPY FL. Horn makes the use of a single label explicit in example 5, where a modified Taqman assay is taught in which an

oligonucleotide singly labeled with BODIPY FL is used without the use of a quencher dye (see column 17, lines 50-55).

(b) Incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to a portion of said one or more target nucleic acid molecules (see columns 17 and 18)

(c) detecting the presence or absence or quantifying the amount of the target molecules by measuring the fluorescent label (see columns 17 and 18).

With regard to claims 14, 15, Horn teaches measurement of the fluorescence during PCR (see column 17, example 5), during LCR (see example 7, column 18) and during SDA (see example 9, column 19).

With regard to claims 17, 19, 59, Horn teaches the use of hairpin oligonucleotides (see figure 4, panel B, for example).

With regard to claim 18, Horn teaches appliication of the method to PCR (see column 2, line 55, for example).

With regard to claims 66, 67, Horn teaches placing the dye at the 3' termini (see column 13, line 39).

Horn expressly teaches application of the method to the use of hairpins and expressly references using Tyagi type molecular beacons with a single fluorescent bodipy label (see columns 17 and 18, example 6).

Horn does not teach incorporation of the hairpin primer into the PCR product and Horn does not teach each possible location of the internal base.

Tyagi teaches the use of hairpin primers (see column 18, example 5) and expressly teaches the use of fluorescently labeled molecular beacon primers being incorporated into the PCR product (see column 18, example 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the single label method of Horn with the hairpin primers of Tyagi since Horn notes "When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube. See, Tyagi et al. (1996) Nature 14:303-308 (see column 18, lines 4-7)." Further motivation to use the modify the Tyagi primers to use a single label is present when Horn notes "Accordingly, single label quenching molecular beacons can be used for the detection of nucleic acids in homogeneous assays and in living cells, as well as for real time monitoring of assays in which nucleic acids are being synthesized, e.g., polymerase chain reactions (see column 18, lines 43-47)." So an ordinary practitioner is motivated to substitute the single label quenching beacons of Horn in the method of Tyagi so that a separate quenching dye is not necessary (see column 18, line 32). Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in

the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

Allowable Subject Matter

6. Claims 21, 22 and 76-79 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. The following is a statement of reasons for the indication of allowable subject matter: In the absence of any evidence, the ordinary practitioner would expect that all fluorescent labels would function equally well in this assay. However, Horn specifically teaches that "Extensive quenching was observed with the BODIPY FL-labeled oligomer, in contrast to the fluorescein- and Texas Red-labeled oligomers which did not show an noticeable quenching under the same hybridization conditions (see column 14, lines 23-27)." In contrast, Applicant's specification expressly shows that each of the claimed labels, including fluorescein and rhodamine, function in the assay. Given direct experimental evidence demonstrated by Applicant, opposed by just a negative teaching of Horn that is not supported by data, the claims are found to be enabled. However, the negative teaching by Horn qualifies under MPEP 2145 as a direct teaching away from

the use of these labels. Consequently, there is no case of prima facie obviousness due to the express teaching away of the Horn reference for use of fluorescein and Texas-red type labels, and no reasonable expectation that other labels would therefore function in the claimed assay. For these reasons, the indicated claims drawn to the specific labels, are objected to as discussed above.

Response to Arguments

8. Applicant's arguments filed November 14, 2005 have been fully considered but they are not persuasive.

Applicant's amendment has overcome most of the 102 rejections (except for claim 20) and the 112, first paragraph rejection, since the claims are now limited to fluorescent labels. Further, the previous rejection over Horn alone required that the nucleic acid serve as the "label" being incorporated for claims 11 and 12. However, given the amendment to limit the claims to "fluorescent" labels, this interpretation is no longer tenable and the new 103 rejection over claims 11 and 12 is necessitated by this amendment.

Applicant's arguments are otherwise addressed to rejections which are no longer pending and are therefore moot in view of the new grounds of rejection.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman

12/27/06

JEFFREY FREDMAN
PRIMARY EXAMINER